Neurobiology of Addiction & Recovery

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American Society of Addiction Medicine
Educational Objectives

- Describe anatomy and physiology of reward circuitry
- Rate contribution of SNP genetic variants on patterns of addictive behavior
- Assess patients for reward deficiency syndrome
- Assess set points of self administration to measure tolerance and physical dependence
- Better prepared to discuss medical indications and mechanism of actions of anti-addiction medications
- Apply 12 step sayings and slogans to increase patient understanding of biology of active behaviors
Jellinek Definition of Dependence

Focused on a predictable course of a disease with potential subtypes based on:

– The clinical course
– Hypothesized causes
– Evidence of physiological damage
AA Sayings: Description of Illness

• I didn’t get into trouble every time I drank, but every time I got in trouble I was drinking

• You can always tell an alcoholic, but you can’t tell them much

• Instant A..hole, just add alcohol

• My best friend became my worst enemy

• I did my drinking from Park Avenue to park bench
AA Sayings: Pathophysiology

• I’m a normal person, minus two drinks

• One drink is too many and a thousand is not enough

• Insanity is defined as doing the same thing over and over again, expecting different results

• Alcoholics heal from the outside in, but feel from the inside out

• Alcoholism is the only disease that tells you, you don’t have it

• Death, insanity or recovery
Substance Dependence (DSM-IV)

- Tolerance *
- Withdrawal *
- Loss of control in limiting intake
- Inability to / Persistent desire to cut down or control
- Great deal of time spent obtaining, using, or recovering from (compulsion to seek and take drug)
- Important activities given up or reduced
- Use despite problems caused or exacerbated by use

(*) Diagnosis with physiological dependence
Addiction is a primary chronic disease with genetic, psychosocial and environmental factors influencing its development and manifestations:

- The disease is often progressive and fatal
- It is characterized by continuous or periodic
  - Impaired control over substance use
  - Preoccupation with the drug
  - Use of substances despite adverse consequences
  - Distortions of thinking, most notably denial
The Reward Pathway and Addiction
Multipolar Neuron

- Soma (cell body)
- Dendrites
- Axon (inside myelin sheath)
- Myelin sheath
- Direction of messages
- Terminal buttons
Anatomy of a Typical Synapse

- Microtubules
- Synaptic vesicles
- Button
- Synaptic cleft
- Golgi complex
- Mitochondrion
- Dendritic spine
- Presynaptic membrane
- Postsynaptic membrane
Natural Rewards

Food
Water
Sex
Nurturing
FIGURE 1

Major brain regions with roles in addiction

The prefrontal cortex is the focal area for cognition and planning. The ventral tegmental area (VTA) is associated with reward and addiction.
Fig. 1.

Neuroanatomy of drug craving. Craving-related information is processed by the OFC, ACC, and nucleus accumbens in response to drug-related cues. Craving-related information can be modulated by the external/internal context, stress, and affective states through the hippocampus, insula, central nucleus of the amygdala, and BNST. Activation of the dIPFC produces increased craving by potentiating the response to drug-related cues through its connection with the OFC, ACC, and nucleus accumbens. The vmPFC plays a key role in emotional control and the inhibition of action associated with poor deleterious consequences. CeA, central nucleus of the amygdala; DS, dorsal striatum; GP, globus pallidus; HPC, hippocampus; NAC, nucleus accumbens; Thal, thalamus.

Activation of the dIPFC, OFC, ACC, and VS during craving may reflect increases in the positive or negative reinforcing effects of drug-related cues. The report by Hayashi et al. represents a major step forward in our understanding of the neurobiology of drug craving.
Natural Rewards Elevate Dopamine Levels

**FOOD**

NAc shell

- Empty Box Feeding

**SEX**

DA Concentration (% Baseline)

Sample Number

- ScrScr Bas Female 1 Present
- Scr Bas Female 2 Present

- Mounts
- Intromissions
- Ejaculations

Source: Di Chiara et al.

Source: Fiorino and Phillips
DA Release Pattern in Rats During Sexual Intercourse

- **Male**
- **Female**
- **Resting DA Level**

**Graph Details:**
- **Y-axis:** DA Release (micro dialysis)
- **X-axis:** Time in Minutes
- The graph shows the DA release pattern over time for both male and female rats during sexual intercourse, with a comparison to the resting DA level.
fMRI of Caudate Region of Brain following food, Music & Cocaine

- Persynaptic DA release above rest

- Food: 6
- Music: 9
- Cocaine: 22
Effects of Drugs on Dopamine Release

**AMPHETAMINE**

![Graph showing the effects of amphetamine on dopamine release with time.](image)

**COCAINE**

![Graph showing the effects of cocaine on dopamine release with time.](image)

**NICOTINE**

![Graph showing the effects of nicotine on dopamine release with time.](image)

**MORPHINE**

![Graph showing the effects of morphine on dopamine release with time.](image)

*Source: Di Chiara and Imperato*
Reinforcement: Neurochemical systems

Enkephalin or Dynorphin Inhibitory Neuron

Enkephalin Inhibitory Neuron

Glutamate Excitatory Input

Enkephalin or Dynorphin Inhibitory Neuron

GABA Inhibitory Neuron

Dopamine Neuron

GABA Neuron

Dopamine Neurons

GABA Inhibitory Feedback

GABA-A Receptors

Presynaptic Opioid Receptors (μ, δ?)

κ Opioid Receptors

μ Opioid Receptors

Dopamine Receptors

GABA Neuron

Ventral Tegmental Area (VTA)

Nucleus Accumbens (NAc)
Neuronal Circuit Changes : Drug Use

- Alcohol intoxication causes
  - Increased dopamine in mesocorticolimbic system
  - Increased endorphins in mesocorticolimbic system *
  - Increased GABA in cortical and limbic systems
  - Increased anandamide (endocannabinoid agonist)

- Antagonist medications block acute rewarding effect
  - Endocannabinoid system (Rimonabant)
  - Opioid (Naltrexone, Vivitrol)
  - GABA (flumazinil)
Brain Reward Cascade

- Unhappy Brain
- Happy Brain

From Ken Blum, MD, PhD: Reward Deficiency Solutions System
Paths to Craving Behavior: From Chocolate to Morphine

Genetic Predisposition

Stress

Long term addiction

Decreased Chemical Functioning in the Brain

- Endorphins
- Serotonin
- Dopamine
- Nor epinephrine
- GABA
Pseudo-Happiness came in plant form
Factors Contributing to Vulnerability to Develop a Specific Addiction

use of the drug of abuse essential (100%)

Genetic (25-50%)
- DNA
- SNPs
- other polymorphisms

Drug-Induced Effects (very high)
- mRNA levels
- peptides
- proteomics

Environmental (very high)
- prenatal
- postnatal
- contemporary
- cues
- comorbidity

Kreek et al., 2000
The Human Genome (as currently understood)

- In the human genome, there are ~3 billion bases (nucleotides)
- In humans, there are estimated to be ~30,000 genes (many but not all identified and annotated)
- Each gene is a sequence of bases or nucleotides

Kreek (Rockefeller University) & Hassin (Columbia P&S), 2004
Single Nucleotide Polymorphisms (SNPs) in Genes: Definitions

- **SNP** — a single nucleotide polymorphism, that is, one nucleotide or base of any base pair

- **Allelic Frequency:**
  - <1% low or rare
  - 1–5% intermediate
  - >5% high, frequent

Kreek (Rockefeller University) & Hassin (Columbia P&S), 2004
Control Mechanisms: Genetic Issues

• Biological mechanisms for loss of control
  – Endogenous dopamine deficiency / imbalance
  – Alcoholism metabolism genes – fast and high dose
  – Alcoholism protective gene – ALDH

• Early Onset Addiction
  – High Risk behavior – dopamine deficiency
  – Impulse control and Frontal Lobe Dysfunction
  – Conduct disorder and legal problems
  – High dose and polysubstance pattern
The Dopamine D$_2$ Receptor Gene
The Reward Gene
## PREDICTIVE VALUE USING BAYES THEOREM OF CARRYING THE DRD2 Taq A1 ALLELE

Total Impulsive-compulsive – Addictive Predictive value 74.4%

<table>
<thead>
<tr>
<th>RISK BEHAVIORS</th>
<th>PREDICTIVE VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism (severe)</td>
<td>14.3</td>
</tr>
<tr>
<td>Cocaine (Severe)</td>
<td>12.3</td>
</tr>
<tr>
<td>Polysubstance Abuse</td>
<td>12.8</td>
</tr>
<tr>
<td>Chemical Dependency</td>
<td>28.3</td>
</tr>
<tr>
<td>Overeating (severe)</td>
<td>18.6</td>
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<tr>
<td>Ingestive Behavior</td>
<td>35.0</td>
</tr>
<tr>
<td>ADHD</td>
<td>16.0</td>
</tr>
<tr>
<td>Smoking</td>
<td>41.5</td>
</tr>
<tr>
<td>Pathological Gambling</td>
<td>4.6</td>
</tr>
<tr>
<td>Tourette’s Syndrome</td>
<td>5.6</td>
</tr>
</tbody>
</table>

The assumptions supporting the data are explained in Blum et al. Journal Royal Society of Medicine 1996;89:396-400
Brain Reward Chemistry Differences between those with the DRD2 A2 allele and those with the A1 allele

**DRD2 Taq A2 allele**
- Normal Reward Circuitry
- Healthy Number of Receptor Sites

**Reward Circuits**

**DRD2 Taq A1 allele**
- Reduced Receptor Sites

**Reward Circuits**
$A_2$ Gene = Normal $D_2$ Receptors
$A_1$ Gene = $\frac{1}{3}$ Lower $D_2$ Receptors
Equates to 100,000,000 people living in the USA
A1 = Dopamine Resistance

• Hypodopaminergic Function
  – “I’m a normal person minus two drinks”

• Lower number of dopamine receptors

• Reduced dopamine release

• Impaired dopamine function

• Attraction to fix imbalance by using drugs/behaviors that increase dopamine

• Commonality among addictions – cross addiction, behavioral addictions and eating disorders
Hypodopaminergic Function Impairs Reward-Dependent Behaviors

- Inability to cope with stress
- **Reduction of energy expenditure**
  - Lower BMR (Energy Conservation) and Fatigue
- Increased carbohydrate & fat cravings
- Increased food intake
  - Energy consumption
- Increased blood pressure
- Increased % body fat
- Higher Body Mass Index
- Blunted reward response to pleasurable experiences
- Intensified bingeing behavior
- Addictive behaviors
- Thrill-seeking behaviors
- Impulsive behaviors
- Compulsive behaviors
- Personality disorders
- Poor executive function
- Reduced global cognition
Reward Genes
Dopamine D2 Receptor Gene Variants

Expression

Lowered D2 Receptors
Association and Behavioral Outcome

Reward Deficiency Syndrome

Impulsive Behaviors
- Attention Deficit Hyperactivity
- Tourette's Syndrome
- Autism

Addictive Behaviors
- Severe Alcoholism
- Obesity
- Severe Smoking Abusiveness

Compulsive Behavior
- Pathological Gambling

Personality Disorders
- Conduct Disorder
- Antisocial Personality
- Aggressive Personality

Aberrant Sexual Behavior
### Reward Deficiency Syndrome

<table>
<thead>
<tr>
<th>Addictive Behavior</th>
<th>Impulsive Behavior</th>
<th>Compulsive Behavior</th>
<th>Personality Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Alcoholism</td>
<td>Attention-deficit disorder, hyperactivity</td>
<td>Aberrant sexual behavior</td>
<td>Conduct disorder</td>
</tr>
<tr>
<td>Polysubstance Abuse</td>
<td>Tourette Syndrome</td>
<td>Pathological gambling</td>
<td>Antisocial personality</td>
</tr>
<tr>
<td>Smoking</td>
<td>Autism</td>
<td></td>
<td>Aggressive behavior</td>
</tr>
</tbody>
</table>
>1/3 of the Total US Population Carries the DRD2 A1 Gene

(Over 100,000,000 people)
GARS Study: Candidate Genes

<table>
<thead>
<tr>
<th>GENE/ALLELE</th>
<th>Number of Subjects</th>
<th>Percentage of Low Risk</th>
<th>Percentage of Moderate Risk</th>
<th>Percentage of High Risk</th>
<th>ASI Lifetime Risk Composite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspi MAOA uVNTR</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caspi MAOA uVNTR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5HTTLLR dialletic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD2 Taq1</td>
<td></td>
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<tr>
<td>DRD3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPRM1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABRA3</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>GABRA3</td>
<td></td>
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</tr>
</tbody>
</table>

Percentage of Low Risk: 14%
Percentage of Moderate Risk: 81%
Percentage of High Risk: 5%
ASI Lifetime Risk Composite: 0
# Genetic Addiction Risk Score (ARS)

<table>
<thead>
<tr>
<th>Patient</th>
<th>MAOA</th>
<th>5HTTLPL</th>
<th>5HTTLPR</th>
<th>SLC6A3</th>
<th>DRD4</th>
<th>DRD2</th>
<th>COMT</th>
<th>Any risk allele</th>
<th>SEVERITY *ARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL-1</td>
<td>3R/3R</td>
<td>L/L</td>
<td>L_A / L_A</td>
<td>10R/10R</td>
<td>4R/4R</td>
<td>A1/A2</td>
<td>A/G</td>
<td>+</td>
<td>0.64 -HS</td>
</tr>
<tr>
<td>CL-2</td>
<td>4R/4R</td>
<td>S/L</td>
<td>S/L_A</td>
<td>10R/10R</td>
<td>4R/7R</td>
<td>A1/A2</td>
<td>A/A</td>
<td>+</td>
<td>0.43-MS</td>
</tr>
<tr>
<td>CL-3</td>
<td>4R/4R</td>
<td>S/S</td>
<td>S/S</td>
<td>9R/10R</td>
<td>4R/4R</td>
<td>A1/A2</td>
<td>G/G</td>
<td>+</td>
<td>0.29-LS</td>
</tr>
</tbody>
</table>

*Percentage of severity is calculated based on 14 alleles whereby there are 7 different risk alleles. This is then converted to a fraction which represents the ARS.

Severity score = 1-36% = Low severity; 37-50% = moderate severity; 51-100% = High severity.
Nutrients at Specific Dosages That Improve Gene Expression & Optimize ‘Reward’
Mechanism of Action of Nutrient Ingredients

<table>
<thead>
<tr>
<th>Gras Nutrients</th>
<th>Neurotransmitter Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Phenylalanine</td>
<td>Opioid Peptides</td>
</tr>
<tr>
<td>L-Phenylalanine</td>
<td>Dopamine</td>
</tr>
<tr>
<td>L-Tryptophane</td>
<td>Serotonin</td>
</tr>
<tr>
<td>L-Tyrosine</td>
<td>Dopamine</td>
</tr>
<tr>
<td>L-Glutamine</td>
<td>GABA</td>
</tr>
<tr>
<td>Chromium</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Rhodiola rosea</td>
<td>COMT and MOA</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Enzyme catalyst</td>
</tr>
</tbody>
</table>

*Reproduced from Chen et al. 2011 with permission.
fMRI, qEEG and Relapse Rate in Response to KB 200

**RELAPSE: without vs with SynaptaGenX (SGX) variant**

- **Study 1:** Cocaine & Alcohol (after 10 months) \( p < 0.001 \)
- **Study 2:** Alcohol & Heroin (after 12 months) \( p < 0.001 \)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control (n=15)</th>
<th>Alcohol (n=15)</th>
<th>Alcohol (n=57)</th>
<th>Heroin (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>87</td>
<td>53</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>Alcohol</td>
<td>33</td>
<td>13</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>87</td>
<td>53</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>SGX Variant</td>
<td>33</td>
<td>13</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

**KB200Z normalizes qEEG dysregulation**

KB200Z vs Placebo in Psychostimulant Addicts

- Alpha (12-15 Hz)
- Beta (15-18 Hz)

**Placebo (n=5)**

**KB200Z (n=5)**
Tolerance and Neuroadaptation

Neuroadaptations Are Occurring
Tolerance: Definitions

- Tolerance: The phenomenon of decreased effect with prolonged exposure to a drug
- Acute tolerance: during the time-course of a single exposure to drug
- Chronic tolerance: over repeated use of drug
Tolerance: Cellular Mechanisms

• Early recovery and abstinence
  – Reward threshold increases
    • Set point of Ah increases
  – Endogenous reward system is downregulated and less responsive to internal rewarding stimuli

• Neuronal activity
  – Decreases in dopaminergic and serotonergic transmission in nucleus accumbens during alcohol withdrawal (measured by *in vivo* microdialysis)
  – Decreases in GABAergic transmission during alcohol withdrawal
Tolerance: Change Number of Receptors

Molecular Mechanisms of Neuroadaptation

GABA  Adenyl cyclase  GABA

NMDA  Ca²⁺  cAMP  second messengers

Opiods/DA/CB1  Na⁺/Ca⁺

K⁺

Cl⁻

Protein kinase signal transduction pathways (PKA/ PKC, CaMK, MAPK etc.)

Fos, CREB, ELK-1, Jun (Transcription Factors)

Changes in Gene Expression

Addiction is a Brain Disease

Repeated Drug Exposure...

• Changes “Reward” Set-Point
• Prolonged Dysregulation leads to vulnerability to drug use behavior, long after acute withdrawal.

(Koob, Neuron, 1998)
Hedonic Homeostatic Dysregulation

Hedonic Set Point is Altered with Chronic Drug Use

Initially use to get high...
Now use to get normal.

“Feel good”
“Feel bad”

Normal Affective Response to Drugs/Alcohol
“Cravings”
Altered Dysregulated Set-Point following chronic drug use

(Koob, Science, 1997)

(Blue line: Normal affective response to drugs/alcohol. Red dotted line: Altered dysregulated set-point following chronic drug use.)
Study of GNR-siRNA nanoplex uptake in DAN cells.
DARPP-32 gene silencing efficiency of GNR-siRNAD nanoplex in DAN cells.

Bonoiu A C et al. PNAS 2009;106:5546-5550

©2009 by National Academy of Sciences
Set Points in Self-Administration

• On Signal
  – Description of thoughts, feelings and behaviors that result in “thought of using” or “craving”

• Ah Signal - Euphoria
  – “the high” - The feeling of enjoyment and satisfaction (satiation) “I’ve had enough” is when enough is enough

• Off Signal - Dysphoria
  – Description of thoughts, feelings and behaviors that send a signal of “I’ve had too much”
Set Points of Drug Self Administration

Drug Effect

OD
Nodding
High
Pain relief
Relaxation
Pinned pupils
Comfortable
Drug desire
Craving
Restlessness
Bone Aches
Chills
Nausea
Sweats
Cramps
Diarrhea
Vomiting

Withdrawal
Calibration and Sensitivity of Receptor Systems / Pathways

• Differences in control circuitry due to:
  Relationship between “on, ah, off” signals

  – On signal set too low
  – The setpoint of Ah signal moves higher (tolerance)
  – The “off” signal is set too high
Calibration and Sensitivity of Receptor Pathways in Early Recovery

Changes in sensitivity and calibration of “on, ah, off” signals influence:

- Severity of illness
- Areas of impaired functioning / problems
- Type of treatment
- Duration of treatment
- Quality of recovery (serenity)
- Maintenance of recovery
- Prevention of relapse
# Changes in Set Points in Addiction

<table>
<thead>
<tr>
<th>Non Addict in Pain</th>
<th>Addict in Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>On</td>
<td>Moderate Pain severity</td>
</tr>
<tr>
<td>Ah</td>
<td>Functional Pain Relief</td>
</tr>
<tr>
<td>Off</td>
<td>Negative Side Effects</td>
</tr>
</tbody>
</table>
Neurobiological Basis of Powerlessness

Sensitivity of system (% difference) to notice or measure changes in signal strength

Sensitivity = degree of change necessary to be recognized as a signal
- Signal differential (+ or -) units of measurement
- Difference between on and off signals

If change in signal strength < differential sensitivity
- Below threshold for noticing = no signal
- Above threshold = recognized as signal and response occurs
  - Examples = temperature differential of thermostats (+/- F)
Neurobiological Basis of Powerlessness

Degree of Sensitivity – inherited + acquired

Sense of self-control depends upon measuring changes in neuronal circuitry

• If you are in control, you can measure change
• If you are in control, you can respond to changes

Sense of “out of control” or “loss of control”

• Control = Executive functioning: decisions and judgment
• If you can’t measure changes, you can’t respond to changes and take action to correct
• If executive function impaired, make poor decisions
• Once aware of poor decision making, try harder to control
Neurobiological Basis of Powerlessness

Powerlessness = Can’t control outcome

Step One : Admit you are powerless over alcohol and our lives had become unmanageable

- Widened differential in “on, ah, and off” signals
- Lack of sensitivity of neuronal circuits
- Lessened self control of dose changes over time
- Inability to reliably predict and control outcome of decisions
Powerlessness = Can’t control outcome

Alcoholics and Addicts have a “control disability”

• As control efficiency worsens, efforts to control increase
  – CAGE questionnaire

• As self directed attempts become more “reliably unreliable”
  – Alcoholics and addicts compensate by becoming control freaks
  – Over-reliance upon self inflates ego
  – As belief in self’s ability to control decreases - awareness of control problem increases
Neurobiological Basis of Surrender

Step Two: Came to believe that a power greater than ourselves could restore us to sanity

- A power greater than ourselves = other than ourselves
- Other than = outside of ourselves = external

Calibration: External point of reference against which you compare yourself to

- You cannot calibrate yourself
- You need to request re-calibration from someone or something external to oneself
Neurobiological Basis of Spirituality

Step Three: Made a decision to turn our will and our lives over to the care of God as we understood Him

GOD = Group Of Drunks

Good Orderly Direction

Turn it over
There is a God and I’m not it
If God is your co-pilot, switch seats
If God seems far away, who moved?

AA works for people who believe in God.
AA works for people who don’t believe in God.
AA NEVER works for people who believe they ARE God
Time Course of Healing

• You can get the drugs out of your body but you can’t get them out of your mind
• It takes time to get your brains out of hock
• A journey of a 1000 miles begins with the first step
• One day at a time
• Bring the body and the mind will follow
• Give time time
• Life starts when you stop
Time Course of Resolution

• **Time course of the illness**
  – Elimination rate of drug from brain / tissues
    • Hours = alcohol, inhalents
    • Days = cocaine, opioids, suboxone
    • Weeks = benzodiazepines, methadone
    • Months = THC, phenobarbital, long acting benzos (Librium, valium)

• **Rate of resolution (undoing) of neuroadaptation**
  – Depends upon neuronal circuit
    • Acute withdrawal – objective physiological alterations
    • Post acute withdrawal – subtle subjective signs and symptoms
  – Requires lack of signal to continue neuroadaptation
    • Requires chemical messengers from nucleus to change DNA, RNA and protein synthesis
    • Faster rate of return with total abstinence: Manufacturing analogy
    • May takes months to years depending upon symptom/neuro circuit
Time Course of Resolution

- **Reward Circuitry: Dopamine transporter**
  - Downregulation of dopamine secondary to tolerance
    - Lack of pleasure from normal activities (weak signal strength)
    - Boredom
    - Recovery activities need higher dose and frequency

- **Stress Circuitry**
  - Norepinephrine (adrenaline) and glutamate increased
    - Attracted to high risk situations to feel adrenaline rush

- **Mood symptoms: Serotonin**
  - Depression and anxiety symptoms may peak in early recovery
  - Need to assess and re-assess in first few weeks to differentiate between substance induced mood disorder and clinical depression or anxiety

- **GABA and Glutamate**
  - Anxiety symptoms may predominate when unchecked neuroadaptation from sedative dependence creates increases in Glutamate and decreases in GABA
  - Sleep disturbance
    - Difficulty falling asleep
    - Frequent re-awakenings – lighter grades of sleep
    - Increased dreams – REM Rebound
Neuroadaptation: Time Course of Resolution

Sources: Volkow, et al., Synapse, 11:184-190, 1992
& Volkow, et al., Synapse, 14:169-177, 1993
Methamphetamine abusers have significant reductions in dopamine transporters.

BNL - UCLA - SUNY
NIDA - ONDCP - DOE
Stress lowers brain endorphins and increases craving behavior.
Chronic alcohol lowers brain endorphins

“Too much of a good thing can be toxic”
Opiates and Alcohol
“Common Mechanisms”

**Naloxone Suppression of Ethanol Narcosis**

- * p < .05 > .01
- *

**Graph:**
- 5 mg/kg Naloxone 15 min prior to 5.5g/kg 25% EtOH
- Saline equiv. volume 15 min prior to 5.5g/kg 25% EtOH
Top image: The process begins when a drug or other stimulus raises the level of the brain chemical glutamate. The glutamate in turn stimulates specific sites, called AMPA receptors and NMDA receptors, on the dopamine cells. The two receptors then interact to produce an electrical current that causes dopamine to flow from the cell's reservoir through the cell's membrane into the space outside the cell.

Bottom image: Once LTP has been established, subsequent exposure to the same stimulus results in a higher AMPA current than occurred in response to the initial exposure, resulting in greater dopamine release.

NIDA Notes: Vol. 18, No. 5 (Dec 2003)
Addictive drugs cause long-term potentiation (LTP) in dopamine-releasing cells in the VTA.

LTP primes these cells to release dopamine more abundantly in response to future exposures to the drug.

Stress induces LTP in VTA cells, a possible clue to the long-observed connection between stress and relapse.

Animal Models for “Craving”

- **Stress – induced reinstatement**
  - Activation of CRF and norepinephrine in extended amygdala (central nucleus of amygdala and bed nucleus of stria terminalis)
  - Extended amygdala gets input from cortical areas involved with emotional processing and output to hypothalamus, a structure involved with regulation of basic drives and emotional expression

- **Cue-induced reinstatement**
  - Basolateral amygdala with possible prefrontal cortex

- **Drug-induced reinstatement (priming)**
  - Medial prefrontal cortex/nucleus accumbens/ventral pallidum circuit mediated by glutamate
  - Mechanism of anti-relapse effect of Campral
Cue Induced Relapse Triggers

• Cue Induced Sayings

  – If you hang around long enough in a barber shop, you’ll get a haircut
  – If you don’t want to slip, stay away from slippery places
  – Don’t hang around wet places and wet faces
  – Lead us not into temptation, I can find it myself

  – We are only as sick as our secrets
  – Stick with the winners
  – Seven days without an AA meeting makes one weak
  – Don’t try to clear away the wreckage of the future
  – Nothing is so bad, a drink won’t make it worse
CRAVING INDUCTION IN PET SETTING

N = 13

\( \Delta \text{ CRAVING} \)

Neutral

Cocaine

STIMULI

DOMINION DIAGNOSTICS
The Memory of Drugs

Front of Brain

Amygdala not lit up

Back of Brain

Nature Video

Cocaine Video

Photo courtesy of Anna Rose Childress, Ph.D.
Cocaine Cravings and Euphoria

- **Cue induced cravings caused by activation of dopamine rich mesolimbic pathway** – sets up brain to experience reward and drive goal-directed behavior.

- **Chasing the high**
  - On signal = cravings
  - Off signal = high
  - Repeated doses cause lowering of Ah point and duration of high
  - On signal for cravings increased over successive doses

- **Cocaine dose relieve cravings in same areas of brain**
Cocaine Craving:
Population (Cocaine Users, Controls) x Film (cocaine, erotic)

Cingulate
Ant Cing
IFG

Garavan et al A. J. Psych 2000
fMRI response: Stage of Recovery

- Occipital-temporal-posterior cingulate
- Visual, spatial, and information processing
- Anterior cingulate
- Emotional processing
- Hippocampus and thalamus
- Learning, memory, and emotional
- Dorsal striatum
- Drug seeking and wanting
- Insula
- Emotional wanting
Computerized Audio Analysis of Emotions

Opioid-SUBX patients and self-awareness of emotions compared to GP + AA members.
Addiction is a Brain Disease

One Drink Leads to Many...

“Reinstatement” of Drug Use
Priming

- Using a drug once or in small amounts can prime the response to drugs and lead to relapse
- Rimonabant blocks cue-induced but not stress-induced priming
- Anti-priming medications could keep a “lapse” from becoming a relapse
  - N-acetylcysteine increases glutamate and blocks cocaine-induced priming
  - Oral naltrexone or injection Vivitrol
Focus on the First Drink: Priming

- Keep the plug in the jug
- First things first
- Keep your sobriety first to make it last
- If you play on the railroad tracks, it’s not the caboose that kills you
- Remember you last drunk
- Think through the drink
- Before engaging your mouth, put your mind in gear
- Are you walking towards a drink or away from one?
- SLIP = Sobriety Loses Its Priority
Reinstatement: Relapse

- Animals are given drug in response to lever pressing
- Drug is taken away
- Lever pressing extinguishes
- Drug is reintroduced
- Lever pressing returns at high intensity
Progression of the Disease

**Fact:** Dose of drug and severity of addiction worse after reinstatement
- It’s as if disease had progressed during abstinence
  - It took 10 years for me to get to a fifth a day.
    20 sober years later, I returned to a fifth a day in one week

**Mechanism of Action**
- Similar to antibody memory effect of immunity
- Short interval for neuroadaptation and dependence to re-occur compared to its rate of initial development
- Re-exposure to the drug sends signals to memory areas triggering gene expression for return of neuroadaptation
- Specific anatomical sites and neuronal pathways involving memory circuits and neurotransmitter glutamate
Frontal Lobe Functions

Executive functioning

- Judgment
- Impulse control
- Planning
- Evaluating
- Rationalizing
- Deciding
- Weighing short term and long term
- Remembering past and applying to future
- Predicting and projection into future
- Timing and pacing of tasks
- Inhibiting basic drives
Decision Making: Frontal Lobe Dysfunction

Substance Dependent Patients
Choose immediate gratification despite long term negative consequences

36% = same as controls - Choice 2
23% = Choice 1 - same as brain damaged VM patients
41% = Hypersensitive to pleasure

High physiological responses to high payoff card
Greater excitement when choosing cards from larger reward deck
More willing to accept punishment to obtain a larger reward

NIDA Notes: Vol. 18, No. 4  (Nov 2003)

Choice 1: High immediate reward, poor long winnings
Choice 2: Small immediate reward, modest long term winnings
Inhibitory Deficits in Addiction

• Increased impulsivity
• Adverse life events can increase impulsivity
  – Conflicts, incarceration, homelessness, etc.
• Problems with reversal learning
  – Addicts don’t know they are doing it wrong
  – Perseverate doing the wrong thing
  – “Doing the same thing over and over expecting different results.”
• Inferior frontal gyrus gray matter deficits
• Drugs damage frontal lobe inhibitory systems
  – Can we strengthen these systems with medications and/or therapies?
Early Recovery – drying out (abstinence) vs. sobriety

- Rate of recovery depends upon amount of neuro-adaptation, rate of disappearance, dose of recovery, and environmental support

- Return to baseline – baseline may differ among individuals
  - How fast down the escalator and how many floors until you get off

- Working a recovery program must work on recovery circuitry

- Working recovery and talking recovery
  Do you “Talk the walk, or walk the talk”
Stages of Recovery

• Early Recovery
  – Get drugs out of system - Detoxification
  – Drink refusal skill
  – Abstinence sustaining skills
  – Mood stabilization
  – Craving and trigger control
  – Identification of Distortion of thinking
  – Relapse Prevention
Biologically Based Treatment Strategies

Detoxification

- **Neuroadaptation** (tolerance + physical dependence) results in alterations in set point and sensitivity of On, Ah, and Off Signals

- **Replacement** with drugs that work on altered neurochemical systems stabilizes neuronal balance
<table>
<thead>
<tr>
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<th>Stages of Addiction + Recovery</th>
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<td>Exposure</td>
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<td><strong>Want</strong></td>
<td>Experimentation</td>
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<td><strong>Get</strong></td>
<td>Planning and drug seeking</td>
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<td><strong>Don’t Like</strong></td>
<td>Recovery and self exploration</td>
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Recovery Dose Equivalency

Concept of “dose equivalent” = reduction of withdrawal symptoms by non-drug techniques = social setting detoxification, supportive care

- Need to try non-pharmacological approaches
  - Change setting – go for a walk, exit strategies, re-arrange living environment
  - Asking for help
    - Calling sponsor
    - Speaking about feelings
  - Exercise
  - Attending meetings
  - HALT techniques
  - Hot baths / showers
  - Massage
  - Meditation, visualization

- Other pharmacotherapies
  - NSAID
  - Mood stabilizers
  - Antidepressants
  - Sleeping aids (often unnecessary when buprenorphine dose is adequate)
Detox Schedule

Rate Dosage Adjustment + Recovery Skill Acquisition

Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6
--- | --- | --- | --- | --- | ---
Dose Drug | Dose Recovery

Graph showing the distribution of dose drug and dose recovery across weeks.

DOMINION DIAGNOSTICS
Spirituality as necessary for recovery

- Metabolotropic receptors
- Dose equivalency of recovery
- Recovery tools and induction of brain changes
- Neuroplasticity and recovery
- Paradox, pleasure and pain
- Neurobiology of recovery and PET scans of internal reward satisfaction
- Loss of contextual placement = loss of sensitivity of person in relationship to places and things
Recovery: Changing Your Brain

• Increase dose and frequency of recovery activities
  – 90 meetings in 90 days
  – 20/20: Come 20 minutes before the meeting, stay 20 minutes after
  – Keep coming back, it works if you work it

• Insert pause in between thought and feeling
  – Call your sponsor before, not after, you pick up a drink
  – Help is only a phone call away
  – The 500 pound phone
  – Easy does it, but DO it
Recovery: Problem Solving Tools

• Change response of thought into action
  – Act as if
  – You are not required to like it, you’re only required to Do it
  – Identify, don’t compare
  – The first step in overcoming mistakes is to admit them

• Recalibrate by talking to others
  – Take the mess to your sponsor, take the message to the meeting
  – The smartest thing an AA member can say is, help
  – Write a gratitude list and count your blessings
  – Ask us how we did it, then do what we did
One Day at a Time

Break intervals into smaller and smaller units

- Counteracts projection into future
  - Thought of never being able to use again, makes me want to use more
- Smaller intervals increases sensitivity
  - Overwhelmed = too long an interval
- Breaks connection between thoughts of using and behavior of using
  - In active addiction, thoughts of using = attempt to use = use
  - In active recovery, urges and cravings are NOT followed by use
  - Extinguishment of signal (thoughts of using) from behavior results in symptom improvement over time
- Establishes recovery dose response relationship
  - If you get through it, your chances of getting through it again go up
Direct Instruction: How It Works

- To thine own self be true
- Spirituality is the ability to get our minds off ourselves
- Humility is our acceptance of ourselves
- Formula for failure: try to please everyone
- We’ll love you, until you learn to love yourself
- HOW – Honesty, Open-mindedness, Willingness
- ISM = I, Self, ME
  - Incredibly Short Memory
  - I Sabotage Myself
Role Modeling and Expert Guide

- Stick with the winners
- Sponsors: have one, use one, be one
- Pass it on
- Share your happiness
- My sponsor says I’m trying. Very Trying
- You can’t give away what you don’t have
- Get to a meeting early and go to the meeting after the meeting
- It’s easy to talk the talk, but you have to walk the walk
- When all else fails, follow directions
- AA is a education without graduation
Spirituality : Outside of Self

• Where you go, there you are
• Spirituality is the ability to get our minds off ourselves
• Faith is spelled a-c-t-i-o-n
• It isn’t the load that weigh us down – it’s the way we carry it
• Principles before personalities
• When you do all the talking you only learn what you already know
• Religion is for those who fear Hell, spirituality is for those who have been there
• There is a God and I’m not it
• There are not atheists in foxholes
• AA never opened the gates of heaven to let me in, AA did open the gates of hell to let me out
• There is not chemical solution to a spiritual problem